194 Serum Sodium

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Definition

Sodium concentration is maintained in a narrow range of 137 to 142 mEq/L of plasma. The value is 145 to 155 mEq/L of plasma *water*, a point to be noted because in a few circumstances there are significant changes in the plasma water concentration.

Technique

The introduction of flame photometry in the late 1940s made measurement of the sodium concentration a practical, reliable laboratory determination. Increasing clinical experience with abnormalities in sodium concentration followed and stimulated studies that have helped explain the control of the plasma sodium level and the pathogenesis of changes in its value. The flame photometer has been replaced by automated methods using ion-specific sodium electrodes that provide equally or more reliable measurement of the plasma sodium concentration.

Basic Science

Disturbances of the serum sodium concentration are often seen in hospitalized patients and may provide the clinician valuable inferences as to the nature or severity of the underlying disease process. It is necessary to stress the conceptual importance of distinguishing between the body sodium *content* and the *concentration* of sodium in body fluids. Active, energy-requiring processes at the cell boundary exclude sodium from the intracellular compartment and, for practical purposes, confine it to the extracellular fluid. Its concentration there is governed by addition or removal of water from the extracellular compartment. Changes in the content of sodium stimulate addition or removal of water and thus determine the volume of the extracellular fluid.

Two mechanisms serve to maintain the plasma sodium concentration in a narrow range in the healthy subject. They are thirst and antidiuretic hormone (arginine vasopressin) release. The concentration of osmotically active plasma solutes, of which sodium is the most important, govern these controls. The contribution of sodium to plasma osmolality is apparent from the formula for calculating plasma osmolality.

$$\text{Plasma osmolality} = 2P_{Na+} + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8}$$

or, substituting normal values:

$$2(140) + \frac{90}{18} + \frac{14}{2.8} = 290$$

In the absence of hyperglycemia or renal failure, the sodium concentration is the chief determinant of plasma osmolality. With a rise in osmolality, antidiuretic hormone release and subsequently thirst is stimulated so that the organism conserves water by reducing urinary excretion of water to a minimum and seeks and drinks water to restore plasma osmolality to normal (Figure 194.1). Of these two controlling systems, thirst is more important. Even in the absence of antidiuretic hormone with resulting inability to conserve water, the thirst drive is sufficient to allow maintenance of a normal plasma sodium concentration, albeit at the expense of the nuisance of polydipsia and polyuria. Only when such a patient is denied access to water or is unable to obtain water because of unconsciousness or disability does the serum sodium concentration rise, resulting in hypernatremia. In this situation of pure water deficit, the amount of sodium in the extracellular fluid is normal, but its concentration is increased. Dilution of body solute by water, as with excessive water or overly vigorous administration of

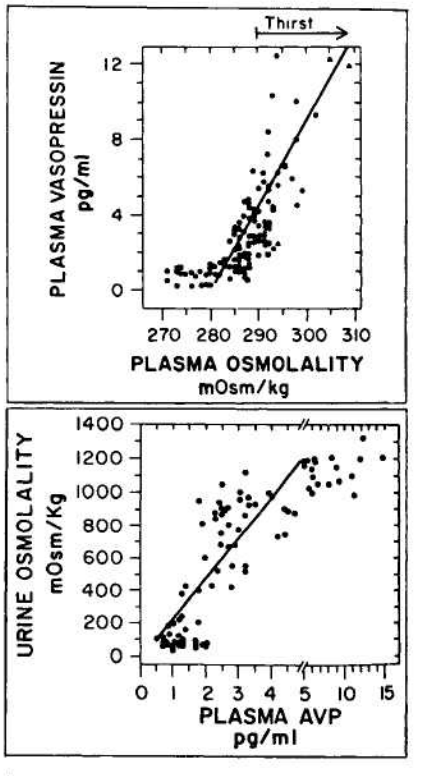

Figure 194.1
Relationship between plasma osmolality and plasma vasopressin levels and thirst. The lower panel shows the relationship between vasopressin (plasma AVP) and urine osmolality. (Reproduced with permission from Robertson GL, Ayeinena P, Zerbe RL. Neurogenic disorders of osmoregulation. Am J Med 1982;72:340.)

intravenous fluids, leads to inhibition of antidiuretic hormone release and water diuresis, again restoring plasma osmolality to normal.

In addition to the osmolar control of vasopressin release, a sizable contraction of the extracellular fluid volume in the range of 8 to 10% may also trigger release of vasopressin and conservation of water. A decrease in the *effective blood volume,* even when the total extracellular fluid volume is increased, may have the same effect.

If the normal mechanisms controlling release of antidiuretic hormone are disturbed for any reason—associated diseases, profound changes in volume of the extracellular fluid, or administration of certain drugs—water may be retained and dilution of the plasma solutes (i.e., hyponatremia), will result, even if the sodium content of the extracellular fluid is normal. With water deficit, plasma sodium *concentration* rises; with water excess, it falls regardless of the extracellular fluid *content.* Even though the plasma sodium concentration tells us nothing about *extracellular* fluid volume, it allows an inference regarding *intracellular* volume. Increase in plasma sodium (plasma osmolality) attracts water out of the cell, leading to shrinkage of the intracellular volume. Hyponatremia (decreased plasma osmolality) allows the flow of water into the cell and expands intracellular volume.

Since sodium is a major osmotically active particle and since changes in osmotic activity govern thirst and antidiuretic hormone release with consequent gain or loss of water, it may be seen that sodium content is the key factor in controlling the volume of the extracellular fluid. Gain of sodium leads to seeking and retaining water with expansion of the extracellular fluid volume. Loss of sodium, at least initially, leads to loss of water and contraction in the extracellular fluid volume. Thus, sodium metabolism governs the volume of the extracellular fluid.

In health, expansion of the extracellular fluid volume leads to renal sodium excretion; contraction of the extracellular fluid volume leads to renal conservation of sodium. To be more precise, we should say contraction of the *effective* extracellular fluid volume or blood volume. The *effective* blood volume is difficult to define exactly, but seems to relate best to adequate filling of the arterial circuit. This requires maintenance of an adequate cardiac output, an adequate intravascular volume, and normal peripheral resistance. A reduced cardiac output, hypoalbuminemia with reduction in blood volume, or an arteriovenous fistula all serve to diminish the "fullness" of the circulation, and any of these conditions may lead to sodium retention. Such abnormalities, when extreme, may signal not only sodium retention but also antidiuretic hormone release that may lead to water retention and hyponatremia. When this occurs, the amount of sodium in the extracellular fluid is increased, but the concentration is reduced.

Thus, water metabolism governs the concentration of the extracellular fluid, whereas sodium metabolism governs the volume of the extracellular fluid.

Clinical Significance

Hypernatremia

Only rarely does hypernatremia result from an excess of sodium. It is virtually always due to a deficit of water. Nevertheless, absolute sodium excess has occurred in infants given excessive salt in their formulas, and occasionally in patients who have been given large amounts of hypertonic sodium bicarbonate during resuscitation after cardiopulmonary arrest.

Hypernatremia due to water deficit is exemplified by the patient with impaired or absent antidiuretic hormone release (central diabetes insipidus) or inability of the kidney to respond to antidiuretic hormone (nephrogenic diabetes insipidus). These two are rather special situations and are not common.

Most cases of hypernatremia seen in hospital practice are elderly patients with varying degrees of impairment of mental function, often residents of nursing homes. The pathogenesis of hypernatremia in this clinical setting is not inability to conserve water but either an impaired thirst drive or debility with inability to obtain water. Such patients, unless malnourished, can concentrate the urine normally, but if disabled or bedridden, are dependent on attendants to provide water. If the amount of water provided is inadequate, especially if insensible losses are increased by fever or high environmental temperatures, hypernatremia results. Occasional patients may have no perception of thirst even with increases in plasma osmolality, but this is the less common mechanism.

Symptoms of hypernatremia (and of hyponatremia) are of central nervous system origin and consist of changes in thought processes and in the level of consciousness. They presumably relate to changes in volume of the cells of the central nervous system (shrinkage with hypernatremia and swelling with hyponatremia), particularly if the condition has developed rapidly. In hypernatremic patients, disturbed consciousness leading to stupor or confusion compounds the problem because the patient is even less likely to seek or request water, so water deficit and hypernatremia worsen. This sequence may progress to irreversible neurologic damage and death. Treatment consists of administration of solute-free water to restore plasma sodium and osmolality to normal.

Many patients with either hypo- or hypernatremia are asymptomatic. The two features that are of the greatest importance in determining the presence or absence of symptoms are the degree of the abnormality and the rapidity with which the change has developed. Symptoms attributable to changes in sodium concentration are unusual unless the sodium level is below 125 or above 160 mEq/L. Symptoms may be seen, however, with lesser abnormalities when they have developed in a few hours.

Hyponatremia

Variations in plasma water may produce apparent but not actual abnormalities in plasma sodium, spurious hyponatremia. In hyperlipidemic states or with pronounced hyperproteinemia, water content per unit volume of plasma is reduced. In these conditions the plasma sodium concentration per liter of *plasma water* is normal, but because of the reduction in water content, the sodium concentration per liter of *plasma* is reduced. Osmotic activity is normal and thirst and antidiuretic hormone release mechanisms are undisturbed. The importance of the condition lies in its recognition, so it will not be confused with other hyponatremic states.

Hyponatremia may occur with the addition of other osmotically active particles such as glucose in uncontrolled diabetes mellitus or exogenous solutes like mannitol or glycerol, which are used as an osmotic diuretic or to lower in-

traocular pressure in glaucoma, respectively. In both these examples the presence of an osmotically active solute confined to the extracellular compartment attracts water out of the cell diluting extracellular fluid and lowering the sodium concentration. Despite a reduced sodium concentration osmolality is normal or increased; this state could be termed *hypertonic hyponatremia.*

In most instances, hyponatremia indicates hypotonicity, that is, water excess for the amount of sodium present. When isotonic hyponatremia (hyperlipidemia or dysproteinemia) and hypertonic hyponatremia (hyperglycemia or exogenous solute) have been eliminated, it may be concluded that disproportionate water retention has occurred and that hypotonic hyponatremia is the result. Analysis of the pathogenesis and management of hyponatremia in this circumstance is best approached by assessment of the extracellular fluid volume (Table 194.1). Assessment of the extracellular fluid and intravascular volume is a clinical, not a laboratory, determination, although certain laboratory data (blood urea nitrogen and uric acid level) may be of assistance.

The features separating patients with hyponatremia into different categories based on the extracellular fluid volume are outlined in Table 194.1. Consider first those patients with an expanded extracellular fluid volume. The most important point to note is the presence or absence of edema or ascites, or signs of congestive heart failure such as a gallop rhythm or basilar rales. In patients with congestive heart failure or with cirrhosis and ascites, the appearance of hyponatremia is a relatively late development, so there is usually a history of preexisting edema or dyspnea to aid the physician. In these states, the edema fluid has the same sodium concentration as the plasma; the total body sodium is increased. Disproportionate retention of water, however, has led to dilution of the extracellular fluid solute, hence the term sometimes applied to this disorder, *dilutional hyponatremia.* Although the mechanism of hyponatremia in these patients has been a topic of debate in the past, it appears that in most instances release of antidiuretic hormone due to a reduction in the effective intravascular volume is the major contributor to water retention. Skilled clinicians have learned that these patients excrete water loads poorly and that infusion of solute-free water, 5% dextrose in water, or hypotonic saline, may produce or aggravate hyponatremia. Management depends on improvement in the underlying disease or restriction of water intake. This approach is appropriate if hyponatremia is severe (less than 120 mEq/L) or is symptomatic (altered level of consciousness).

Contrast these patients with those who have become depleted of sodium and are hypovolemic. When sodium is lost from the extracellular fluid, there is initially loss of water and extracellular fluid volume is reduced. Loss of water occurs because sodium loss decreases plasma osmolality and thus inhibits vasopressin release. In addition, reduced osmolality of the extracellular fluid leads to movement of water into the intracellular space. With moderate sodium losses, water is lost proportionately, and the plasma sodium concentration remains normal. If the sodium losses continue and exceed approximately 200 mEq, the reduction in the extracellular fluid and plasma volume become sufficient to trigger release of antidiuretic hormone. If the patient drinks water or is given hypotonic fluid, the water is not excreted. Tonicity is sacrificed for volume, water is retained, and hyponatremia results. Teleologically, this is an eminently sound mechanism. If water losses continued *pari passu* with sodium, hypotension, impaired cerebral and coronary perfusion, and ultimately death would result. "Better alive with hyponatremia than dead with a normal serum sodium."

In this condition, appropriate management is clear: re-

Table 194.1
Classification of Hyponatremia

	Clinical features	Laboratory features
Hyponatremia with expanded extracellular fluid volume (excess total body sodium)		
Causes		
Congestive heart failure	Edema, rales, gallop rhythm	Urine Na^+ <10 mEq/L
Cirrhosis	Ascites	BUN to creatinine ratio often >10:1
Nephrotic syndrome	Edema	Hyperuricemia in congestive heart failure
Hyponatremia with contracted extracellular fluid volume (reduced total body sodium)		
Causes: renal loss of sodium		Urine Na^+ may be elevated May have hypokalemic alkalosis
Overtreatment with diuretics		
Sodium restriction in chronic renal failure		BUN to creatinine ratio may be >10:1
Addison's disease		
Causes: extrarenal losses	No edema May have postural hypotension	Urine Na^+ low BUN to creatinine ratio may be >10:1
Vomiting, diarrhea		
Burns		
Extensive trauma		
Peritonitis		
Hyponatremia with normal or slightly expanded ECF volume (normal or slightly reduced total body sodium)		
Causes		
Syndrome of inappropriate antidiuretic hormone release	No edema	Urine Na^+ >30 mEq/L Low BUN Low uric acid level (<4.5 mg/dl)
Drugs that impair water excretion		

placement of sodium and water losses. Replacement is usually given with isotonic sodium solutions; normal saline or one-half normal saline to which 45 mEq of sodium bicarbonate has been added is often used. Symptomatic hyponatremia is uncommon in this setting, but if present, treatment with hypertonic saline is warranted.

If water is retained in the absence of sodium deficit and in the presence of a normal circulation, there is slight expansion of the extracellular fluid volume and dilution of solutes, so that hyponatremia results. Such a state may be mimicked by giving vasopressin in oil to a normal subject over a period of several days. More important for clinicians, this state may be produced by sustained, autonomous release of vasopressin in the absence of the normal physiologic stimuli, that is hyperosmolarity or hypovolemia. In this sense, the release of vasopressin is inappropriate, thus the generic name applied to this disorder: the syndrome of inappropriate antidiuretic hormone release (SIADH). Since the initial description of this entity in 1957, numerous cases of SIADH of widely diverse causes have been recognized. Sustained release of vasopressin leads to water retention so that plasma sodium concentration is reduced. Extracellular fluid volume is expanded, resulting in sodium excretion in the urine and concentration of the urine (i.e., the urine is hypertonic to plasma and remains so despite additional water ingestion and further hyponatremia). A wide variety of causes of this syndrome has been identified. The more common ones are listed in Table 194.2.

It is this group of hyponatremic patients who are more likely to have symptomatic hyponatremia requiring treatment. Confusion, belligerent behavior, stupor, coma, and seizures may be seen with progressive hyponatremia, particularly if the plasma sodium concentration has fallen rapidly. The approaches to treatment include:

- Acute
  - —Hypertonic saline
  - —Hypertonic saline plus furosemide
- Chronic
  - —Water restriction
  - —Demeclocycline
  - —Furosemide

Of these, the most rapidly effective in the symptomatic patient is infusion of hypertonic saline coupled with furosemide. For chronic control of symptomatic hyponatremia, both demeclocycline and oral furosemide have been successful. Mild or moderate hyponatremia, levels above 125 mEq/L, if asymptomatic and stable, do not require treatment.

Table 194.2
More Frequently Encountered Causes of SIADH

Pulmonary
Carcinoma
Pneumonia
Granulomatous diseases
Central nervous system
Meningitis
Trauma
Tumors
Encephalitis
Systemic
Postoperative state
Protracted vomiting

If hyponatremia is corrected to normal or near normal levels within a few hours, particularly when the hyponatremic state has been of several days' duration, a syndrome characterized by profound neurologic disability may result. Manifestations range from mild weakness and behavioral changes to quadriplegia with inability to swallow or speak. The morphologic change of note is loss of myelin in certain areas of the central nervous system, particularly the pons, hence the name central pontine myelinolysis. The role of the rate of correction of hyponatremia in this syndrome is debated. Since elevation of the plasma sodium concentration by only 5 or 6 mEq/L in patients with symptomatic hyponatremia usually reverses the neurologic abnormalities, further rapid elevation of the sodium level is not necessary and may be harmful.

Miscellaneous Disorders

Some additional causes of hyponatremia should be mentioned. In patients with acute oliguric renal failure, infusions of hypotonic solutions (5% dextrose in water or hypotonic saline) will inevitably lead to hyponatremia unless those solutions are being given to replace known losses. In this situation, the administered water "has no place to go," and dilution of plasma sodium is the result.

Psychotic patients sometimes drink large amounts of water, upward of 8 to 10 L per day. They may present with hyponatremia, seizures, and stupor. The pathogenesis is not clear in many of these patients, although reduction of water intake usually corrects the hyponatremic state and reverses the symptoms.

Treatment with thiazide diuretics impairs the ability to excrete water. They should not be prescribed in compulsive water drinkers because symptomatic hyponatremia with coma or seizures can result. A similar sequence may be observed in elderly patients given thiazide diuretics or given hypotonic fluids in the postoperative period. Certain drugs may also impair water excretion and lead to hyponatremia:

- Chlorpropamide
- Clofibrate
- Carbamazepine
- Vincristine
- Cyclophosphamide

Finally, the plasma sodium level is reduced by about 4 mEq/L during pregnancy. The mechanism of this reduction is not apparent.

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